REMARKS

Claims 1 and 3-20 were at issue. Claims 1 and 3-20 were rejected. The Examiner made the following rejections / objections:

I. Claims 1, 3-10 are allegedly rejected under 35 U.S.C. § 112 ¶ 2 as being indefinite for failing to distinctly claim the subject matter.

II. Claims 10-20 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Pat. No. 4,647,675 To Mayer et al., in view of U.S. Pat. No. 4,900,686 To Arnost [Earnest] et al., and U.S. Pat. No. 5,846,737 To Kang [King].

Applicants believe the present amendments and the following remarks traverse the Examiner's rejection of the claims. These remarks are presented in the same order as they appear above.

I. The Claims Are Definite

A. Covalent Bonding Is Properly Supported By The Specification

The Examiner states that, "[t]he phraseology 'under covalent bonding conditions', claim 1, line 26, is not defined in the claim so as to ascertain the metes and bounds of the invention." *Office Action, Mailed February 05, 2002, pg 2.* The Examiner goes on to qualify this conclusory statement with the proposition that the claims, "... must recite reagents, the reaction times, and conditions...". *Id.* The Examiner's position is clearly contrary to well settled law which supports the Applicants proposition that the invention as claimed need be read in view of the specification. That is to say, "[i]t is entirely proper to use the specification to interpret what the patentee meant by a word or phrase in the claim." *E.I. du Pont de Nemours & Co. v. Phillips Petroleum Co.*, 849 F.2d 1430, 1433 (Fed. Cir. 1988). Moreover the meaning of the terms in the claims may be ascertainable by reference to the description. *See, 37 C.F.R. §1.75(d)(1).*

In specification of the application as filed the Applicants note that, "conjugation is preferably via a phosphoramidite linkage when synthesizing labeled oligonucleotides, and may be by a variety of the known protein conjugation chemistries when synthesizing labeled

peptides or labeling." *Application (as filed on June 25, 1999), p. 3, ll. 25 - 28.* In Example 11 (of the application as filed) the Applicants teach the linkage, via a covalent reaction, of an organic compound (bovine serum albumin) with a fluorophore (rhodamine) to form a labeled protein. *Id. at pp. 27 - 28.* The Applicants respectfully submit that these teaching, cited from the specification, render definite the phase, "under covalent bonding conditions" as recited in the pending claims.

Additionally, the Applicants object to the Examiner's invocation of *Ex parte Fressola* to support the pending rejection under 35 U.S.C. § 112 ¶ 2. Specifically, the Examiner states that, "[a] claim **must stand alone** to define the invention[], and incorporation into the claims by express reference to the specification or an external source **is not permitted**". See, *Office Action pg. 3* [emphasis added]). The Applicants respectfully submit that the holding in Fressola is of no moment in view of the Applicants' pending claims.

In *Ex parte Fressola*, the BPAI considered the relationship between the specification and *omnibus* claims. That is to say, the BPAI stated:

> "Claims in utility applications ... that **define the invention entirely by reference** to the specification and/or drawings, so-called "omnibus claims" or "formal" claims ... are properly rejected under § 112 ¶ 2 as failing to point out and distinctly claim the invention". *Ex parte Fressola, 27 USPQ 1608, 1609 (BPAI, 1993).* [emphasis added]

None of the Applicants' pending claims, however, may be properly characterized as "omnibus" claims. An omnibus claim is characterized by such hallmark language as "the invention substantially shown or described" or "any and all features of novelty described, referred to, exemplified, or shown". The Applicants, in contrast, have claimed their invention with such detail such that the first independent claim provides 25 lines of typewritten description. This degree of description particularly points out and distinctly claims the claimed embodiments of the present invention.

Nonetheless, without acquiescing to the Examiner's argument and in order to further the prosecution [while expressly reserving the right to prosecute the original (or similar) claims in subsequent applications] Applicants have amended claim 1, to recite that conjugation occurs at a functional group of the R_a, substituent, in order to clarify one embodiment of the present invention.

B. Claim 1 And Claim 10 Are Definite

The Examiner states that, "[t]he terms 'organic compound' ... and 'biomolecule' ... renders the claims indefinite." *Office Action, pg 3.* While the Applicants believe this language cited by the Examiner is definite they have, without acquiescing to the Examiner's argument and in order to further the prosecution (while expressly reserving the right to prosecute the original (or similar) claims in subsequent applications), amended claims 1 and 10 while cancelling (without prejudice) claims 3, 4, and 9.

Claim 1 now incorporates the limitations of the cancelled dependent claims (e.g. claim 3, 4, and 9) while claim 10 has been amended, as suggested by the Examiner, to replace the term "fluorescent" with "fluorophore". The Applicants. therefore, respectfully request the Examiner to withdraw the pending rejection under 35 U.S.C. § 112 ¶ 2.

II. The Claims Are Not Obvious

The Examiner states that "Claims 10-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mayer et al., US 4,647,675, in view of Arnost [Earnest] et al., US 4,900,686, and Kang [King] US 5,846,737.

A. The Examiner Continues To Ignore His Burden

i. The Examiner Recycles The Same Flawed Rejections

In their papers filed on February 23, 2001 and October 23, 2001, the Applicants set out the standards (under the law) the Examiner must meet in order to establish a *prima facie* case of obviousness. Subsequently, the Applicants provided a detailed analysis documenting how: i) the Examiner failed to provide (any evidence based) motivation to combine the references, ii) even if improperly combined the cited references do not teach each element of the claims, iii) U.S. patent 4,647,645 is non-analogous art, and iv) the other references cited by the Examiner teach different conjugates. Instead of substantively rebutting the Applicants' arguments (in the pending Office Action), the Examiner: i) recycles (almost verbatim) the same "103" rejections offered in the previous two Office Actions and ii) cites case law to, incorrectly, support the *non sequitur* that is the Examiner's pending rejection under 35 U.S.C. § 103. The Applicants stand on their arguments, set out in their papers

captioned above, and believe these same arguments defeat all pending rejections under 35 U.S.C. § 103.

ii. The Authority Cited By The Examiner Does Not Relieve The Examiner's Obligation To Establish A Prima Facie Case Of Obviousness.

The Examiner states that Applicants' previous arguments are not persuasive because;

> "...applicants cannot show nonobviousness by attacking references individually where the rejection is based on combinations of references. See *In re Keller,* 642 F.2d 1091 ...; *In re Merck & Co.,* 800 F.2d 1091 ...". *Office Action. pg 5.*

Through these remarks, the Examiner appears to suggest that the previous rebuttal(s) to the alleged *prima facie* case of obviousness were limited to Mayer *et al.* The Examiner misapprehends the file history.

The Applicants note that *In re Keller* only applies to arguments, in rebuttal to a *prima facie* case of obviousness, **IF** these same arguments are based *on only one* of several references cited by an Examiner. That is to say,

> "As characterized by the appellant, the [ ] affidavit offered as objective evidence of non-obviousness concerns itself mainly with the question of whether the Walsh et al. article suggest[s] ... [however] the test is not whether a suggestion to use digital timing ... is found in Walsh ... but rather what Keller in view of Walsh and what Berkovits in view of Walsh would have suggested to one of ordinary skill in the art.
>
> *In re Keller*, 642 F.2d 413, 426 (CCPA 1981).

Similarly, the holding in *In re Merck* (in part) relies on *In re Mapelsden* where the Court clearly states that all references must be analyzed;

> The issue lies in what the combination of references makes obvious to the person of ordinary skill and not whether a feature of one reference can be bodily incorporated in the other to produce the subject matter claimed. *In re Henley*, 44 CCPA 701, 239 F.2d 399, 112 USPQ 56. *In Re Mapelsden*, 51 C.C.P.A. 1123; 329 F.2d 321; 1964 CCPA LEXIS 440; 141 U.S.P.Q. (BNA) 30 (CCPA 1964).

Turning to the file history in the instant case, the Applicants in previous (and present) arguments rebut, with specificity, all of the art raised by the Examiner in the rejections under 35 U.S.C. § 103. Specifically, as noted above, the Applicants' have (in part) argued that Mayer *et al.* is **non-analogous art** and that Arnost *et al.* and Kang *et al.* teach conjugates having **a different chemical synthesis basis** (i.e., lactam ring formation and sulfate

conjugates). In addition, the Applicants have scrupulously documented the Examiner consistent failure to provide any evidence based motivation for combination of the cited art.

Furthermore the Applicants prior analysis also documents how specific elements of the Applicants' preferred embodiment are lacking from ALL THE REFERENCES. That is to say, even if the Examiner asserts the Applicants' have allegedly "attacked the references individually", the Examiner has still failed to properly assert a *prima facie* case of obviousness. Specifically, the Examiner's attempted obviousness rejection fails the *prima facie* test on (at least) two out of the three Federal Circuit prongs. *In re Vaeck*, 947 F.2d 488, 20 USPQ.2d 1438 (Fed. Cir. 1991); and *MPEP* § 2142; Establishing A *Prima Facie* Case Of Obviousness.

First, Mayer *et al.* provides no motivation or suggestion for the conjugation of rhodamine and, therefore, cannot be properly combined with either Arnost et al. or Kang. Second, all three references lack a teaching that prevents lactam ring formation during the conjugation of rhodamine at a 3-carboxylamide position. The Examiner is reminded that if ONLY ONE of the above requirements is not met, then a *prima facie* case of obviousness may not be established.

The Applicants respectfully request the Examiner to reconsider the previous rebuttal of the *prima facie* case of obviousness and that the pending rejection under 35 U.S.C. 103 be withdrawn.

CONCLUSION

The Applicants believe the arguments and amendments, set forth above, traverse the Examiner's rejections. The Applicants respectfully request that all pending rejection be withdrawn and that the application be passed to allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, the Applicant encourages the Examiner to call the undersigned collect at 617.252.3353.

Dated: August 5, 2002

Thomas W. Brown
Registration No. 50,002

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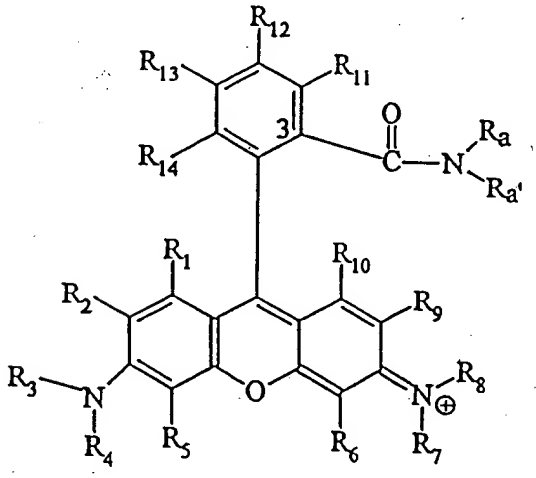
APPENDIX I
MARKED-UP VERSION OF REWRITTEN CLAIMS
PURSUANT TO 37 CFR § 1.121 (c)(1)(ii)

1. A method of labeling an organic compound for fluorescent detection, comprising:

providing a fluorophore having the structure illustrated by Formula A

FORMULA A



where R_1 and R_{10} taken alone are hydrogen or halogen; R_2, R_5, R_6 and R_9 taken alone are hydrogen, alkyl, carboxyalkyl, aminoalkyl, alkylether, alkylthioether, halogen or alkoxy; R_3, R_4, R_7 and R_8 taken alone are hydrogen, and substituted or unsubstituted alkyl, carboxyalkyl, aminoalkyl, cycloalkyl, aryl; R_2 and R_3 taken together are alkyl chains each having from 2 to 5 carbon atoms connecting the 2′ carbon to the nitrogen attached to the 3′ carbon; R_9 and R_8 taken together are alkyl chains each having from 2 to 5 carbon atoms connecting the 7′ carbon to the nitrogen attached to the 6′ carbon; R_4 and R_5 taken together are alkyl, each having from 2 to 5 carbon atoms connecting the 4′ carbon to the nitrogen attached to the 3′ carbon; R_6 and R_7 taken together are alkyl, each having from 2 to 5 carbon atoms connecting the 5′ carbon to the nitrogen attached to the 6′ carbon; R_3 and R_4 taken together form an alkyl or alkylene chain containing up to 5 atoms in the principal chain,

consisting of carbon and one or more heteroatoms from the group consisting of nitrogen or oxygen, with both terminal valence bonds of said chain being attached to the nitrogen attached to the 3′ carbon; R_7 and R_8 taken together form an alkyl or alkylene chain containing up to 5 atoms in the principal chain, consisting of carbon and one or more heteroatoms from the group consisting of nitrogen or oxygen, with both terminal valence bonds of said chain being attached to the nitrogen attached to the 6′ carbon; R_{11}, R_{12}, R_{13}, and R_{14} are each hydrogen or halogen, where R_a and $R_{a'}$ are selected from the group consisting of alkyl, carboxyalkyl, aminoalkyl, cycloalkyl, aryl and arylalkyl, [non-hydrogen substituents], wherein R_a confers resistance to lactam ring formation, and further wherein $R_{a'}$ contains a functional group; and,

conjugating the fluorophore with [an organic compound] a biomolecule selected from the group consisting of an amino acid, peptide, protein, nucleotide, oligonucleotide, nucleic acid, cell surface membrane and viral coat [to be labeled under covalent bond forming conditions, the conjugating] through the $R_{a'}$ functional group of the fluorophore, the resultant conjugate being fluorescent upon excitation with light of a determinable wavelength.

5. The method as in claim [3] 1 wherein the biomolecule is attached to a solid support.

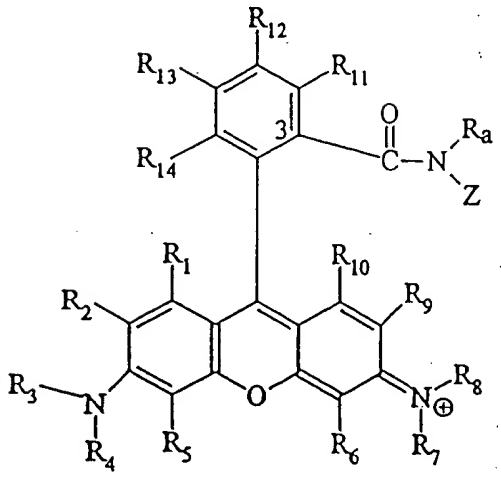
6. The method as in claim [3] 1 wherein the biomolecule is an oligonucleotide and the fluorophore is attached via a phosphoramidite at the 5′ end in the conjugate.

8. The method as in claim [3] 1 wherein the biomolecule is an amino acid, a peptide or a protein, and the fluorophore is attached at an amine or sulfhydryl in the conjugate.

10. A [fluorescent] fluorophore conjugate comprising:

a conjugated substance and a fluorophore, the conjugated substance being an amino acid, peptide, protein, nucleotide, oligonucleotide, or nucleic acid to which is attached one or more fluorophores, the [fluorescent] fluorophore conjugate having the structure illustrated by Formula 1

FORMULA 1



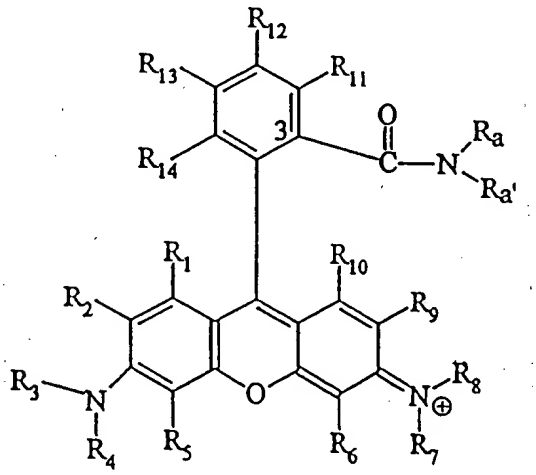
where R_1 and R_{10} taken alone are hydrogen or halogen; R_2, R_5, R_6 and R_9 taken alone are hydrogen, alkyl, carboxyalkyl, aminoalkyl, alkylether, alkylthioether, halogen or alkoxy; R_3, R_4, R_7 and R_8 taken alone are hydrogen, and substituted or unsubstituted alkyl, carboxyalkyl, aminoalkyl, cycloalkyl, aryl; R_2 and R_3 taken together are alkyl chains each having from 2 to 5 carbon atoms connecting the 2′ carbon to the nitrogen attached to the 3′ carbon; R_9 and R_8 taken together are alkyl chains each having from 2 to 5 carbon atoms connecting the 7′ carbon to the nitrogen attached to the 6′ carbon; R_4 and R_5 taken together are alkyl, each having from 2 to 5 carbon atoms connecting the 4′ carbon to the nitrogen attached to the 3′ carbon; R_6 and R_7 taken together are alkyl, each having from 2 to 5 carbon atoms connecting the 5′ carbon to the nitrogen attached to the 6′ carbon; R_3 and R_4 taken together form an alkyl or alkylene chain containing up to 5 atoms in the principal chain, consisting of carbon and one or more heteroatoms from the group consisting of nitrogen or oxygen, with both terminal valence bonds of said chain being attached to the nitrogen attached to the 3′ carbon; R_7 and R_8 taken together form an alkyl or alkylene chain containing up to 5 atoms in the principal chain, consisting of carbon and one or more heteroatoms from the group consisting of nitrogen or oxygen, with both terminal valence bonds of said chain being attached to the nitrogen attached to the 6′ carbon; R_{11}, R_{12}, R_{13}, and R_{14} are each hydrogen or halogen, where R_a is an alkyl, carboxyalkyl, aminoalkyl, cycloalkyl, aryl, or arylalkyl having from 1 to 10 carbon atoms, and Z represents a linker plus the conjugated substance, wherein said conjugated substance lacks a lactam ring.

APPENDIX II
CLEAN VERSION OF THE ENTIRE SET OF PENDING CLAIMS
PURSUANT TO 37 CFR § 1.121 (c)(3)

1. A method of labeling an organic compound for fluorescent detection, comprising:

providing a fluorophore having the structure illustrated by Formula A

FORMULA A



where R_1 and R_{10} taken alone are hydrogen or halogen; R_2, R_5, R_6 and R_9 taken alone are hydrogen, alkyl, carboxyalkyl, aminoalkyl, alkylether, alkylthioether, halogen or alkoxy; R_3, R_4, R_7 and R_8 taken alone are hydrogen, and substituted or unsubstituted alkyl, carboxyalkyl, aminoalkyl, cycloalkyl, aryl; R_2 and R_3 taken together are alkyl chains each having from 2 to 5 carbon atoms connecting the 2′ carbon to the nitrogen attached to the 3′ carbon; R_9 and R_8 taken together are alkyl chains each having from 2 to 5 carbon atoms connecting the 7′ carbon to the nitrogen attached to the 6′ carbon; R_4 and R_5 taken together are alkyl, each having from 2 to 5 carbon atoms connecting the 4′ carbon to the nitrogen attached to the 3′ carbon; R_6 and R_7 taken together are alkyl, each having from 2 to 5 carbon atoms connecting the 5′ carbon to the nitrogen attached to the 6′ carbon; R_3 and R_4 taken together form an alkyl or alkylene chain containing up to 5 atoms in the principal chain, consisting of carbon and one or more heteroatoms from the group consisting of nitrogen or oxygen, with both terminal valence bonds of said chain being attached to the nitrogen

attached to the 3′ carbon; R_7 and R_8 taken together form an alkyl or alkylene chain containing up to 5 atoms in the principal chain, consisting of carbon and one or more heteroatoms from the group consisting of nitrogen or oxygen, with both terminal valence bonds of said chain being attached to the nitrogen attached to the 6′ carbon; R_{11}, R_{12}, R_{13}, and R_{14} are each hydrogen or halogen, where R_a and $R_{a'}$ are selected from the group consisting of alkyl, carboxyalkyl, aminoalkyl, cycloalkyl, aryl and arylalkyl, wherein R_a confers resistance to lactam ring formation, and further wherein $R_{a'}$ contains a functional group; and,

conjugating the fluorophore with a biomolecule selected from the group consisting of an amino acid, peptide, protein, nucleotide, oligonucleotide, nucleic acid, cell surface membrane and viral coat through the $R_{a'}$ functional group of the fluorophore, the resultant conjugate being fluorescent upon excitation with light of a determinable wavelength.

5. The method as in claim 1 wherein the biomolecule is attached to a solid support.

6. The method as in claim 1 wherein the biomolecule is an oligonucleotide and the fluorophore is attached via a phosphoramidite at the 5′ end in the conjugate.

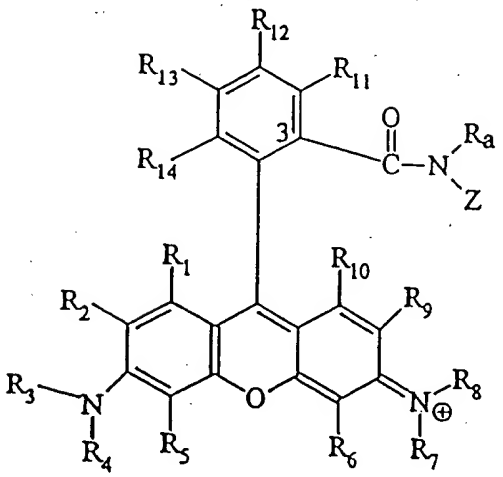
7. The method as in claim 5 wherein the biomolecule is an oligonucleotide and the fluorophore is attached at the 3′ end in the conjugate.

8. The method as in claim 1 wherein the biomolecule is an amino acid, a peptide or a protein, and the fluorophore is attached at an amine or sulfhydryl in the conjugate.

10. A fluorophore conjugate comprising:

a conjugated substance and a fluorophore, the conjugated substance being an amino acid, peptide, protein, nucleotide, oligonucleotide, or nucleic acid to which is attached one or more fluorophores, the fluorophore conjugate having the structure illustrated by Formula 1

FORMULA 1



where R_1 and R_{10} taken alone are hydrogen or halogen; R_2, R_5, R_6 and R_9 taken alone are hydrogen, alkyl, carboxyalkyl, aminoalkyl, alkylether, alkylthioether, halogen or alkoxy; R_3, R_4, R_7 and R_8 taken alone are hydrogen, and substituted or unsubstituted alkyl, carboxyalkyl, aminoalkyl, cycloalkyl, aryl; R_2 and R_3 taken together are alkyl chains each having from 2 to 5 carbon atoms connecting the 2′ carbon to the nitrogen attached to the 3′ carbon; R_9 and R_8 taken together are alkyl chains each having from 2 to 5 carbon atoms connecting the 7′ carbon to the nitrogen attached to the 6′ carbon; R_4 and R_5 taken together are alkyl, each having from 2 to 5 carbon atoms connecting the 4′ carbon to the nitrogen attached to the 3′ carbon; R_6 and R_7 taken together are alkyl, each having from 2 to 5 carbon atoms connecting the 5′ carbon to the nitrogen attached to the 6′ carbon; R_3 and R_4 taken together form an alkyl or alkylene chain containing up to 5 atoms in the principal chain, consisting of carbon and one or more heteroatoms from the group consisting of nitrogen or oxygen, with both terminal valence bonds of said chain being attached to the nitrogen attached to the 3′ carbon; R_7 and R_8 taken together form an alkyl or alkylene chain containing up to 5 atoms in the principal chain, consisting of carbon and one or more heteroatoms from the group consisting of nitrogen or oxygen, with both terminal valence bonds of said chain being attached to the nitrogen attached to the 6′ carbon; R_{11}, R_{12}, R_{13}, and R_{14} are each hydrogen or halogen, where R_a is an alkyl, carboxyalkyl, aminoalkyl, cycloalkyl, aryl, or arylalkyl having from 1 to 10 carbon atoms, and Z represents a linker plus the conjugated substance, wherein said conjugated substance lacks a lactam ring.

11. The conjugate as in claim 10 wherein the conjugated substance is bound to the fluorophore through an amide, ester, ether, disulfide, or thioether linkage.

12. The conjugate as in claim 10 wherein the linkage between the fluorophore and conjugated substance has a phosphate ester.

13. The fluorescent conjugate as in claim 10 wherein the conjugated substance is attached to a solid support.

14. The fluorescent conjugate as in claim 13 wherein the solid support is controlled pore glass.

15. The fluorescent conjugate as in claim 13 wherein the solid support is a polymer support.

16. The fluorescent conjugate as in claim 10 wherein the conjugated substance is part of a cell membrane.

17. The fluorescent conjugate as in claim 10 wherein the conjugated substance is part of a viral coat.

18. The fluorescent conjugate as in claim 10 wherein the fluorophore is derived from tetramethylrhodamine.

19. The fluorescent conjugate as in claim 10 wherein the fluorophore is derived from rhodamine 101.

20. The fluorescent conjugate as in claim 10 wherein the fluorophore is derived from rhodamine B.